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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,339	10/25/2004	Koji Teshima	2004-1514A	5677

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,339	TESHIMA ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-13 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-13 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 10-13, 21-27 are pending in the current application.

2. This application is a national stage of PCT/JP03/03925 filed March 28, 2003. and claims priority to Japanese Application 200293398 filed March 29, 2002. The priority documents have been received and the boxes on the PTO-326 from have been checked as per applicant's request.

Response to Arguments

3. Applicant's arguments filed on December 26, 2007 have been fully considered but they are not fully persuasive. Rejections of cancelled claims are withdrawn. However, with respect to the rejection under 35 U.S.C. 103 (a) for obviousness, the rejection of claims 10-13 has changed in light of new art discovered by the examiner. It was not pointed out by the applicant, but the examiner actually applied art relating to piperidinyl-benzimidazolones bearing hexahydrophenalene (the Jenck PNAS reference). This was not the closest prior art since applicant's claims are drawn to compounds bearing the acenaphthalene group on the piperidine ring. The examiner apologizes for this clear error and now makes a new 103(a) rejection below in light of the newly discovered art. The affidavit under 37 CFR 1.132 filed December 26, 2007 is insufficient to overcome the rejection of claims based upon the new grounds of rejection as set forth in the last Office action because the previous 103(a) rejection is withdrawn and the affidavit attempts to compare compounds other than those that form the basis of the new grounds of rejection. This action is NON-FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of compounds bearing multiple substitutions for treating a various sleep disorders. **(B) The nature of the invention:** This is a medicinal invention requiring the synthesis of compounds and use of the compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing physician or pharmacist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Medicine and in particular treating sleep disorders is unpredictable (*see below*) **(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** ORL-1 antagonists may no doubt have a utility, however the use of

these compounds in the treatment of sleep disorders has not been shown. The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). One reviewer put it this way:

> "Although one may successfully identify substances that effect circadian rhythmicity when the biochemical milieu of the clock is successfully manipulated, one is immediately faced with several problems in generalizing from those changes to the clinical situation. First, most of the peptides and neurotransmitters listed in Table 1 are not unique to the SCN and are often relatively ubiquitous in their CNS distribution. They are involved in the regulation of a number of more complex behaviours, as well as physiological and endocrinological processes. Therefore, by some means, a chronobiotic would have to stimulate the SCN selectively, leaving the same transmitter and peptide systems in the rest of the brain stimulated. Second, when light induces phase-shifts, several transmitter systems may act synergistically, and this synergistic interaction could be quite complex. Therefore, administration of a drug affecting a single transmitter system may have little effect on SCN output. Third, ideally the chronobiotic would have to be administered orally, for convenience, but survive gastric digestion. At the same time, the peripheral nervous system and visceral organs would have to remain unaffected. Finally, many compounds may affect complex behavioural systems, such as thought, cognition, and motivational states. Inferring a chronobiotic effect for a drug on the basis of an action on complex cognitive or behavioural systems will always be problematic unless nondrug interventions that produce similar behavioural changes are also considered chronobiotic. While it is apparent that powerful chronobiotics are now on the threshold

> of discovery, a great deal of work has to be conducted on aspects of dose and timing. The possibility of tolerance developing with prolonged use is pertinent to choice of doses. Despite these barriers, as the applied application and commercial advantages of any chronobiotic is large, there undoubtedly will be an intensification of research for other compounds in the foreseeable future." Drew Dawson and Stuart Maxwell Amstrong "Chronobiotics-Drugs That Shift Rhythms" *Pharmacology and Therapeutics* **1996**, *69*, 15-36.

The endogenous ligand for ORL-1, N/OFQ an agonist, is known to have many functions related to anxiety, pain and other physiological processes. It seems very unlikely that a medical doctor or Pharm. D. would know what to do with these compounds. Indeed one reviewer remarked: "When treating sleep disorders of the circadian kind, special care must be given to distinguish compounds with chronobiotic properties from those with hypnotic effects. Whereas a chronobiotic may induce sleep by shifting the sleep–wake cycle so that sleep onset occurs earlier, a hypnotic will simply induce sleep without affecting the circadian mechanism." Yvan Touitou, André Bogdan "Promoting adjustment of the sleep–wake cycle by chronobiotics" *Physiology & Behavior* **2007**, *90*, 294–300. These compounds are active at the opioid like receptor which may mean that they are causing a simple sedative or hypnotic effect. The correlation between the activity disclosed in the specification and the treatment of sleep disorders is absent. The factors outlined in *In Re Wands* mentioned above apply here. It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation for the plethora of sleep disorders mentioned.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

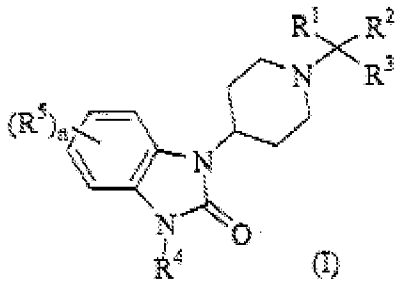
5. Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over unpatentable over Ito, F. et. al. 1999 WO 9936421 A1 AND Tulshian, D. et. al. WO 2000006545 in view of Goehring et. al. U.S. 6,635,653 (cited on the IDS) OR Hashiba et. al. "Characterisation and comparison of novel ligands for the nociceptin/orphanin FQ receptor" *Naunyn-Schmiedeberg's Archives of Pharmacology*, **2001**, *363*, 28-33 OR Roever et. al. "High-Affinity, Non-Peptide Agonists for the ORL1 (Orphanin FQ/Nociceptin) Receptor" *Journal of Medicinal Chemistry* **2000**, *43*, 1329-1338 OR Adam et. al. U.S. 6,113,527 OR Wichmann, Jurgen et. al. "8-Acenaphthen-1-yl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one derivatives as orphanin FQ receptor agonists." *Bioorganic & Medicinal Chemistry Letters*, **1999**, *9*, 2343-2348. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Ito, F. et. al. teaches a large group of 1-piperidin-4-yl-2-benzimidazolone ORL-1 receptor agonists. The 89 compounds of Table 1 (pg. 59 are shown below)

TABLE



(I)

Example No.	R^1	R^2	R^3	R^4	R^5
1	cyclohexyl		Ph	H	H
2	cyclohexyl		benzyl	H	H
3	cyclohexyl		methyl	H	H
4	cyclohexyl		ethenyl	H	H
5	cyclohexyl		2-thienyl	H	H
6	cyclohexyl		ethynyl	H	H
7	cyclohexyl		propyl	H	H
8	cyclohexyl		4-Cl-Ph	H	H
9	cyclohexyl		4-methoxy-Ph	H	H
10	methyl	methyl	Ph	H	H
11	methyl	methyl	benzyl	H	H
12	methyl	methyl	2-thienyl	H	H
13	methyl	methyl	4-F-Ph	H	H
14	methyl	methyl	4-methyl-Ph	H	H
15	methyl	methyl	3-Ph-propyl	H	H
16	methyl	methyl	4-methoxy-Ph	H	H
17	cycloheptyl		Ph	H	H
18	cycloheptyl		2-thienyl	H	H
19	ethyl	ethyl	Ph	H	H
20	ethyl	ethyl	2-thienyl	H	H
21	cyclobutyl		Ph	H	H
22	cyclobutyl		2-thienyl	H	H
23	cyclopentyl		Ph	H	H
24	cyclohexyl		Ph	H	6-Cl
25	cycloheptyl		Ph	H	6-Cl
26	cyclopropyl		Ph	H	H
27	cycloheptyl		Ph	methyl	H
28	cycloheptyl		Ph	H	5-methoxy
29	dimethylcyclohexyl		Ph	H	H

TABLE (continued)

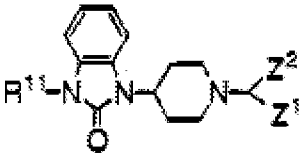
Example No.	R^1	R^2	R^3	R^4	R^5
30	cyclononyl		n-propyl	H	H
31	bicyclo[4.3.0]nonan-8-yl		Ph	H	H
32	cyclooctyl		Ph	H	H
33	cyclononyl		Ph	H	H
34	cyclodecyl		Ph	H	H
35	cycloundecyl		Ph	H	H
36	cyclododecyl		Ph	H	H
37	cycloheptyl		4-F-Ph	H	H
38	cycloheptyl		3-F-Ph	H	H
39	cycloheptyl		4-methoxy-Ph	H	H
40	cycloheptyl		3-methoxy-Ph	H	H
41	cycloheptyl		2-methoxy-Ph	H	H
42	4-t-butylcyclohexyl		Ph	H	H
43	cycloheptyl		Ph	H	4-F
44	cycloheptyl		Ph	H	5-F
45	cycloheptyl		Ph	H	6-F
46	cycloheptyl		Ph	H	5-Me
47	cycloheptyl		Ph	H	6-Me
48	cycloheptyl		Ph	H	5-CF_3
49	cycloheptyl		Ph	H	Ph-CO-
50	cycloheptyl		Ph	H	7-Cl
51	cycloheptyl		Ph	H	5,6-di-F
52	cycloheptyl		Ph	H	5,6-di-Cl
53	spiro[5.5]undecan-3-yl		propyl	H	H
54	isopropylidenecyclohexyl		propyl	H	H
55	cyclononyl		methyl	H	H
56	cyclononyl		ethyl	H	H
57	cyclooctyl		methyl	H	H
58	cyclooctyl		ethyl	H	H
59	cyclooctyl		propyl	H	H
60	cyclohept-4-enyl		Ph	H	H
61	cyclohept-4-enyl		methyl	H	H
62	cyclohept-4-enyl		ethyl	H	H
63	cyclohept-4-enyl		propyl	H	H
64	cycloheptyl		Ph	aminoethyl	H
65	cycloheptyl		Ph	guanidinoethyl	H
66	cycloheptyl		Ph	methylaminoethyl	H
67	cycloheptyl		Ph	acetylaminoethyl	H
68	cycloheptyl		Ph	L-prolinamidoethyl	H

TABLE (continued)

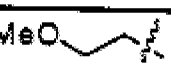
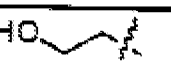
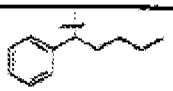
Example No.	R^1	R^2	R^3	R^4	R^5
69	cycloheptyl		Ph	pyridyl-CONH-ethyl	H
70	cycloheptyl		Ph	aminopropyl	H
71	cycloheptyl		Ph	aminohexyl	H
72	cycloheptyl		Ph	piperidinoethyl	H
73	cycloheptyl		Ph	morpholinoethyl	H
74	cycloheptyl		Ph	dimethylaminoethyl	H
75	cycloheptyl		Ph	diisopropylaminoethyl	H
76	cycloheptyl		Ph	piperidinylethyl	H
77	cycloheptyl		Ph	pyrrolylethyl	H
78	cycloheptyl		Ph	piperazinoethyl	H
79	cycloheptyl		Ph	pyridinylpropyl	H
80	cycloheptyl		Ph	amidinopiperazinoethyl	H
81	cycloheptyl		Ph	n-butyl	H
82	cycloheptyl		Ph	benzyl	H
83	cycloheptyl		Ph	NH_2-CH_2CONH-$(CH_2)_2$-	H
84	cycloheptyl		Ph	aminoacetylpiperazinoethyl	H
85	cycloheptyl		Ph	methylsulfonylaminoethyl	H
86	cycloheptyl		Ph	acetyl	H
87	cycloheptyl		Ph	pyrimidinylaminoethyl	H
88	cycloheptyl		Ph	pyrimidinylpiperazinoethyl	H
89	cyclohept-4-enyl		Ph	aminoethyl	H

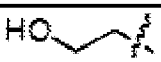
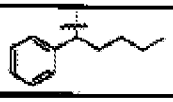
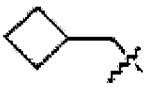
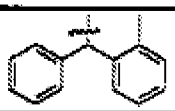
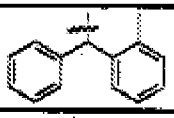
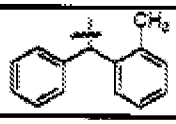
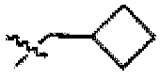
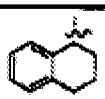
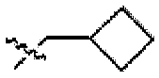
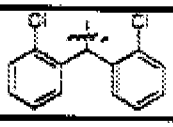
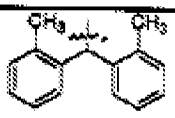
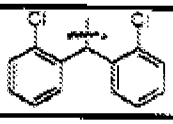
Tulshian et. al. also teaches a large group of 1-piperidin-4-yl-2-benzimidazolone ORL-1 receptor agonists. The 50 or so compounds of Table 5 (pg. 38-41 38) are shown below:

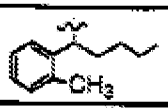
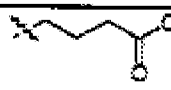
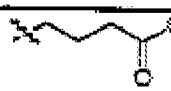
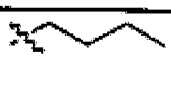
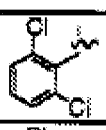
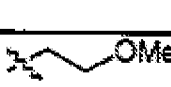
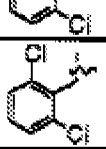
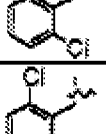
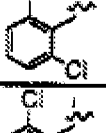
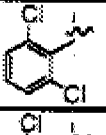
Table 5



wherein R^{11}, Z^1 and Z^2 are as defined in the following table, wherein Ac is acetyl, Me is methyl and Et is ethyl::

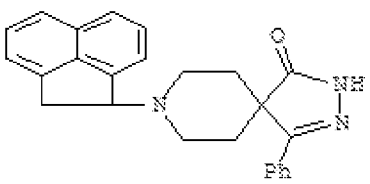
R^{11}	$CH(Z^1)(Z^2)$	Physical Data
H	Benzhydryl	
	Benzhydryl	$C_{32}H_{37}N_3O$:HCl CI 480 (100), 167.25 (22)
	Benzhydryl	$C_{29}H_{31}N_3O_3$:HCl CI 470.15 (100), 167.25 (25)
	Benzhydryl	$C_{29}H_{31}N_3O$:HCl CI 438.20 (100), 167.25 (29)
	Benzhydryl	$C_{30}H_{33}N_3O$:HCl FAB 452.3 (100), 167.0 (92)
	Benzhydryl	$C_{29}H_{33}N_3O$:HCl CI 440.20 (100), 167.25 (22)
Me	Benzhydryl	$C_{25}H_{27}N_3O$:HCl CI 398.15 (100), 167.25 (39)
Ethyl	Benzhydryl	$C_{27}H_{29}N_3O$:HCl CI 412.15 (100), 167.25 (32)
n propyl	Benzhydryl	C28H31N3O:HCl ESI 426.1(14), 167 (100)
n butyl	Benzhydryl	$C_{29}H_{33}N_3O$:HCl ESI 440.10 (100), 167.10 (33)
isopropyl	Benzhydryl	$C_{28}H_{31}N_3O$:HCl ESI 446.10 (28), 167. (100)
MeO 	Benzhydryl	$C_{28}H_{31}N_3O_2$:HCl ESI 442.10 (15), 167. (100)
HO 	Benzhydryl	$C_{27}H_{29}N_3O_2$:HCl FAB 428.3 (65), 232.1 (57)
H		$C_{23}H_{29}N_3O$:HCl ESI 364.1 (58), 218.1 (100)

HO 		$C_{25}H_{33}N_3O_2$:HCl ESI 408.1 (93), 262.1 (100)
n pentyl	Benzhydryl	$C_{30}H_{35}N_3O$:Hcl ESI 454.1 (46), 167.1 (100)
n-hexyl	Benzhydryl	$C_{31}H_{37}N_3O$:HCl ESI 468.1 (26), 167 (100)
	Benzhydryl	$C_{28}H_{31}N_3O_2$:HCl ESI 442.10 (15), 167 (100)
		$C_{31}H_{35}N_3O$:HCl ESI 466.1 (44), 181.1 (100)
MeO 		$C_{29}H_{33}N_3O_2$:HCl ESI 456.1 (48), 181.10(100)
H		$C_{24}H_{31}N_3O$:HCl CI 378.25 (100), 306.20 (22), 218.20 (24)
H		$C_{28}H_{27}N_3O$:HCl ESI 398.10 (44), 181.1 (100)
		$C_{27}H_{33}N_3O$:HCl ESI 416.10(36), 286.1 (39)
		$C_{30}H_{31}N_3OCl_2$:HCl ESI 522.1 (79), 521.1 (48), 520 (100)
	Benzhydryl	$C_{30}H_{34}N_2O$:HCl CI 439.25 (100), 168.30 (20)
H		$C_{27}H_{29}N_3O$:HCl CI 412.20(32), 218.20 (42), 195.35 (100)
	Benzhydryl	$C_{29}H_{31}N_3O_3$:HCl ESI 470.1 (100), 167.1 (77.40)
H		$C_{25}H_{23}N_3Cl_2O$:HCl ESI 452.1 (100), 235 (85)

H		$C_{24}H_{31}N_3O$ FAB 378.4 (100), 218.2 (30)
	Benzhydryl	$C_{31}H_{35}N_3O_3$ 498.2 (100), 167.1 (90)
	Benzhydryl	$C_{29}H_{31}N_3O_3$ ESI 470.1 (100), 167.1 (55)
		$C_{23}H_{27}Cl_2N_3O$ ESI 434.1 (80), 432.1 (100)
		$C_{22}H_{25}Cl_2N_3O_2$ ESI 436.1 (58), 434.1 (100)
		$C_{23}H_{27}Cl_2N_3O$ ESI 434.1 (35), 432.1 (100)
		$C_{24}H_{27}Cl_2N_3O$ ESI 446.1 (77)), 444.1 (100)
		$C_{21}H_{22}Cl_2N_4O_2$ FAB 435.1 (78), 433.1 (100)

Goehring, et. al. U.S. 6,635,653 teaches a compounds that are ORL-1 ligands and very similar to the ones of the instant case. The most potent compound that showed was the compound shown below, which bears the acenaphthalene group:

RN 473909-38-6 CAPLUS
CN 2,3,8-Triazaspiro[4.5]dec-3-en-1-one, 8-(1,2-dihydro-1-acenaphthylenyl)-4-phenyl- (CA INDEX NAME)



Column 22

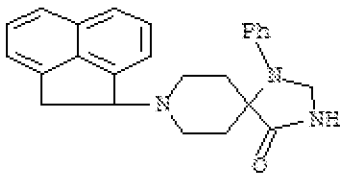
TABLE 1

Nociceptin Affinity

Compound	calc K_i (nM)
8-(acenaphthen-9-yl)-4-phenyl-2,3,8-triazospiro [4.5]dec-3-en-1-one	.06

Hashiba et. al. "Characterisation and comparison of novel ligands for the nociceptin/orphanin FQ receptor" *Naunyn-Schmiedeberg's Archives of Pharmacology*, **2001**, *363*, 28-33 teaches the following compound:

IT 228246-56-8, Ro 65-6570
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(characterization and comparison of novel ligands for nociceptin/orphanin FQ receptor in relation to cAMP formation)
RN 228246-56-8 CAPLUS
CN 1,3,8-Triazaspiro[4.5]decan-4-one, 8-(1,2-dihydro-1-acenaphthylenyl)-1-phenyl- (CA INDEX NAME)

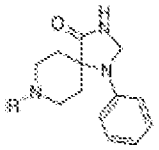


and makes this statement this regarding Ro-65-6570, "Collectively, our data demonstrate that Ro65-6570 is a potent NCR agonist which has high affinity and moderate selectivity for hNCR. Therefore, Ro65-6570 in combination with the growing number of novel NCR ligands [particularly the highly selective and potent non-peptide ligands Ro64-6198 (agonist) and J-

113397(antagonist)] represent important new tools for studies of the physiopathophysiological role(s) played by the NC/NCR system."

Roever, Stephan et. al. "High-Affinity, Non-Peptide Agonists for the ORL1 (Orphanin FQ/Nociceptin) Receptor" *Journal of Medicinal Chemistry* **2000**, *43*, 1329-1338, teaches that the acenaphthalene group is the preferred substituent.

Table 2. Receptor Binding of 1-Phenyl-1,3,8-triazaspiro[4.5]decan-4-ones Substituted with Aryl-cycloalkyl Derivatives on the Piperidine Nitrogen[a]



		K_i (± SEM) [nM]			
compd	R	hORL1	μ	κ	δ
1f	2-tetralinyl	6.3 (2.1)	15.1 (5.5)	47.1 (9.1)	620 (280)
1j	1-tetralinyl	2.1 (0.7)	12.8 (1.4)	10.7 (2.3)	480 (140)
1k	1-indanyl	0.7	3.4 (0.8)	5.3	540 (290)
1m	2-indanyl	2.5	26.0 (0.6)	161	710
1n (*S*)	1-tetralinyl	10.2 (3.7)	13.3 (4.6)	17 (13)	nd
1o (*R*)	1-tetralinyl	2.5 (1.3)	12.3 (2.6)	46.3 (5.2)	530 (160)
1p	5-Me-1-tetralinyl	1.4 (0.4)	31.7 (8.8)	44 (11)	460 (71)
1q	acenaphthenyl	0.52	5.9	26	250

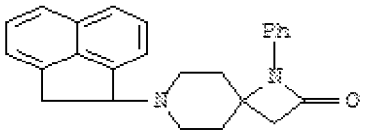
[a] The data are the mean of two to three (± SEM) different binding experiments performed in triplicate. The K_d of the radioligands used were as follows: [^{3}H]-OFQ 70 pM for hORL1 receptors, [^{3}H]-naloxone 1.3 nM for hμ receptors and 2.8 nM for hκ receptors, [^{3}H][Ile^{5,6}]-deltorphin II 0.36 nM for hδ receptors.

The discussion of Roever below is relevant:

"The best selectivity toward dopamine receptors was generally found for compounds which are also selective toward the opioid receptors, such as **1q** (ORL1: 0.52, D2: 520, D3: 1210, D4.4: 350 nM). Affinities Affinities for D1 and 5HT receptors (5HT1DR, 5HT2a, 5HT2c, 5HT6, 5HT7) are low for all these compounds (Ki > 1000nM) Systematic modification of our original lead, **1a**, resulted in the identification of compounds with improved affinity and high potency in the GTPγ–S and cyclase assays. Compounds **1p** and **1q** are moderately selective for OFQ versus the μ and κ receptors and have only low affinity toward δ receptors. These compounds will serve as starting points for further inroads into the development of truly selective non-peptide ORL1 receptor agonists and allow pharmacological characterization of the OFQ/ORL1-receptor system. Indeed **1q**, or more precisely one of its enantiomers, has already been shown to display anxiolyticlike properties in the elevated plus-maze procedure in rats."

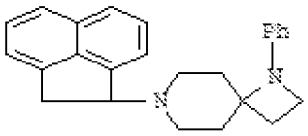
Adam, et. al. U.S. 6,113,527 teaches the following compounds:

RN 254096-96-8 CAPLUS
CN 1,7-Diazaspiro[3.5]nonan-2-one, 7-(1,2-dihydro-1-acenaphthylenyl)-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 254096-97-9 CAPLUS
CN 1,7-Diazaspiro[3.5]nonane, 7-(1,2-dihydro-1-acenaphthylenyl)-1-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

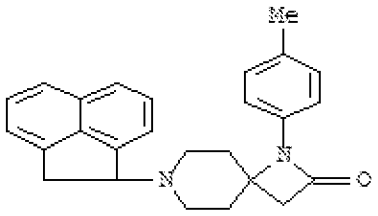


● HCl

RN 254097-25-1 CAPLUS
CN 1,7-Diazaspiro[3.5]nonan-2-one, 7-(1,2-dihydro-1-acenaphthylenyl)-1-(4-methylphenyl)-, (2E)-2-butenedioate (1:1) (CA INDEX NAME)

CM 1

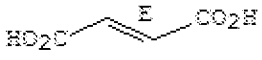
CRN 254097-24-0
CMF C26 H26 N2 O



CM 2

CRN 110-17-8
CMF C4 H4 O4

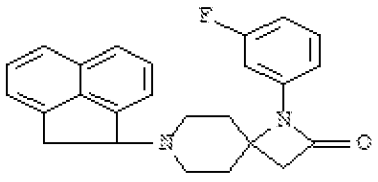
Double bond geometry as shown.



RN 254097-52-4 CAPLUS
CN 1,7-Diazaspiro[3.5]nonan-2-one, 7-(1,2-dihydro-1-acenaphthylenyl)-1-(3-fluorophenyl)-, (2E)-2-butenedioate (1:1) (CA INDEX NAME)

CM 1

CRN 254097-51-3
CMF C25 H23 F N2 O



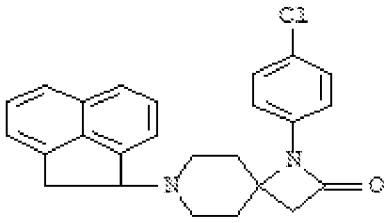
CM 2

CRN 110-17-8
CMF C4 H4 O4

RN 254097-54-6 CAPLUS
CN 1,7-Diazaspiro[3.5]nonan-2-one, 1-(4-chlorophenyl)-7-(1,2-dihydro-1-acenaphthylenyl)-, (2E)-2-butenedioate (4:3) (CA INDEX NAME)

CM 1

CRN 254097-53-5
CMF C25 H23 Cl N2 O



CM 2

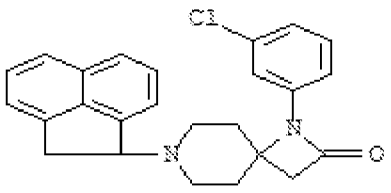
CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

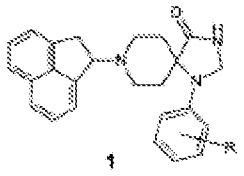
RN 254097-56-8 CAPLUS
CN 1,7-Diazaspiro[3.5]nonan-2-one, 1-(3-chlorophenyl)-7-(1,2-dihydro-1-acenaphthylenyl)-, (2E)-2-butenedioate (1:1) (CA INDEX NAME)

CM 1

CRN 254097-55-7
CMF C25 H23 Cl N2 O



Wichmann, Jurgen et. al. "8-Acenaphthen-1-yl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one derivatives as orphanin FQ receptor agonists." *Bioorganic & Medicinal Chemistry Letters*, **1999**, *9*, 2343-2348, teaches the following compounds, all of which bear the acenaphthalene group:



1

Table 1. Binding affinities (pKi) for human OFQ and opioid (μ,κ,δ) receptors

compound	R	OFQ	μ	κ	δ
1a	H	9.2	8.2	7.6	6.6
1b (S)	H	8.7	7.9	7.6	< 6.3
1c (R)	H	9.6	8.4	7.7	7.0
1d	2-F	7.4	6.4	6.8	n.d.
1e	3-Cl	8.9	7.7	7.3	6.8
1f	3-Me	8.4	8.0	7.7	< 6.3
1g	3-OMe	7.8	7.4	n.d.	n.d.
1h	3-F	9.5	8.4	7.9	6.8
1i	3-Br	8.4	7.9	7.1	< 6.3
1j	3-CF_3	8.0	8.1	n.d.	n.d.
1k	4-Cl	8.8	7.5	7.1	< 6.3
1l	4-Me	8.3	7.3	6.7	< 6.3
1m	4-OMe	7.0	n.d.	n.d.	n.d.
1n	4-F	8.8	7.6	7.2	< 6.3
1o	3,5-diMe	8.0	7.7	n.d.	n.d.

Ascertainment of the difference between the prior art and the claims
(MPEP 2141.02)

Ito et. al. and Talushian et al. do not expressly teach acenaphthenyl for R_1-R_2 or Z1-Z2 respectively, however they teach all the other structural features of the instantly claimed compounds.

All the other references teach compounds similar to those of the instant case, that have the acenaphthenyl group on the piperidinyl nitrogen. This exact modification is what distinguishes the compounds of Ito and Talushian from those of the instant case.

Finding of prima facie obviousness
Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the compounds Ito et. al. and Talushian et al. as suggested by Goehring, Hashiba, Roever, Adam and Wichman to produce the instant invention. One of ordinary skill in the art would have been motivated to do this because the introduction of the acenaphthalene group gave the most potent compounds and selectivity over other opioid receptor subtypes and dopamine receptors. ORL-1 agonists may eventually be valuable for the treatment of disorders thus increasing potency and selectivity is highly desirable. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusions

9. No claims are allowed. This action is NON-FINAL.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625